



Review Article

Cassava, cyanide and hypothyroidism

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ABSTRACT

Cassava (manioc) is an important crop as a basic, starchy energy food for both humans and farm animals throughout the tropics and sub-tropics and it is also exported to temperate regions, but does not seem to receive attention equivalent to that accorded to the other crops in this group. Its status as a good subsistence crop owes something to its self-protection by way of cyanogenic glycosides hydrolysed to release cyanide ions when tissue is damaged and the glycosides are thus placed into contact with an enzyme that hydrolyses them and is also present in the plant tissue. Cyanide toxicity and the toxin's links, proven and possible, with goitre and hypothyroidism are described and their practical significance is discussed. The potential for responses to be changed by deficiencies in nutrients such as Vitamin B12, iodine and certain amino acids, as well as consumers' overall nutrient status, is discussed. Suggestions are offered for future research to clarify significant issues presented from these considerations.

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INTRODUCTION

Cassava, the crop

Cassava is often seen as food for the poorer consumers throughout the tropics and sub-tropics, and it might therefore be supposed that its consumption would decline as affluence increases. In fact its production and consumption seem to be increasing quite sharply, for example threefold in the last 20 years in Africa alone, according to press reports. It is also increasingly important as a feed for animals, and for Thailand, the world's leader in exports of the crop, it is a significant revenue earner. Its capacity to grow and yield useful crops on even fairly marginal soils and habitats, to require relatively little by way of pesticide control, to be reasonably drought resistant, and to be easily propagated by planting cuttings from the stems taken from the plant when the tubers are harvested all make it a fascinating crop that deserves much attention, although at the present time it is in reality rather a "Cinderella" among food plants despite its ranking among the top four bulk human foods along with rice, wheat and maize. In 2000 A.D. (2543 B.E.) the Food and Agriculture Organization of the United Nations initiated a programme to raise its profile, but this seems to have met with relatively little response to date.

Cassava's origins

Wherever it is grown, cassava is generally perceived as an indigenous plant, but in fact it is a relatively recent introduction from South Central America, where it is indeed indigenous and a part of the traditional diet since time immemorial. It is reasonable to think that, like foods such as breadfruit, it was perceived as a cheap energy food for slaves and near-slaves in the colonies belonging to the great European powers. Whatever the reason, it spread rapidly across the tropics and sub-tropics after it came to the attention of the explorers who first made connections between the "Old" and the "New" worlds.

Botany

The Genus *Manihot* is a member of the Order Malpighiales, Family Euphorbiaceae (spurges). It is not clear to me how many species are accepted in the Genus; Wikipedia mentions others in passing but only provides details on *M. esculenta*. Most workers use this species name for both the bitter (high potential cyanide level) and "sweet" (lesser cyanide) varieties, but Steinkraus (2004) reserves the name *M. esculenta* for the sweet varieties and places bitter varieties into *M. palmata* and *M. utilissima*. This issue is not important in the present context, but needs to be noted and should properly be resolved to maintain appropriate scientific precision.

Why this Review?

I was invited to give a presentation under the general topic of food safety and fermentation to the "2nd International Conference on Agriculture and Agro-Industry", and saw this as an excellent opportunity to explore cyanide toxicity and its relationship with hypothyroidism in the context provided by cassava, as an increasingly important world food crop. As I explored the issues in greater detail I became concerned that, while some workers, such as Steinkraus (1998), have attempted to address some issues concerning toxicity, the information seems to be patchy and sometimes confusing. There is gross toxicity, where cyanide levels are such as to pose an immediate danger to health and even to life; this seems to be

well understood by all commentators on these issues. While this is generally agreed it is somewhat more difficult to find consistent opinions as to what constitutes safe exposure limits for those working in an environment where hydrogen cyanide is present in (or may enter) the atmosphere (see Agency for Toxic Substances website; Daniel *et al.*, 2014; USEPA website, for example). However, it is the effects that may arise from lower doses consumed, however, for long periods, up to virtually the whole of the consumer's life that are more interesting here. Steinkraus in particular has noted concerns about goitre ("goiter" in American) an enlargement to the thyroid gland, classically associated with diets deficient in iodine, but found in consumers for whom cassava is a daily staple and whose diets have low general nutritional status. The same worker has recorded some reported cyanide levels in and around places where cassava tubers are being processed. However, it is difficult to find the kind of data for the cassava industry that is available concerning workers in such industries as metal plating processes utilizing cyanides, with daily exposure levels, blood thiocyanate levels and other relevant data pertaining to workers' exposure to cyanides and their bodies' responses thereto (see Banerjee *et al.*, 1997). Other reports on cassava, its cyanide content and physiological effects on consumers thereof include Soto-Blanco *et al.* (2002) who studied the effects of long term but low dose rate inclusion of cyanide in rats' diets. Chandra *et al.* (2003; 2004) examined the interacting effects when cassava was fed to rats along with various iodide levels and also extended consideration of potentially goitrogenic effects to other Indian plant foods known to have cyanogenic activities. An internet "Blog" called *Diagnosis Diet* reviewed a similar theme in a piece entitled "Foods that cause hypothyroidism". An early study on thyroid function in a cassava-eating population (Cliff *et al.*, 1986) considered if there was a relationship with epidemic spastic paraparesis and the cassava consumption by that population, but no really clear trend was observed. Daniel *et al.* (2014) examined cyanide-induced hyperthyroidism in male rats and showed that while rice plus cyanide gave a clinically confirmable effect, feeding cassava representing the same cyanide level and calorie intake did not cause significant damage, a difference that they attributed to the cassava contributing some additional protein to the base diet. While it is not unreasonable to hold that improving the nutrient input and hence the diet's status will give the subjects increased capacity to withstand the poison, cassava is so low in protein that it is a little difficult to accept that it could make that much difference in an otherwise nutritionally balanced diet. Working with dogs, Kamalu and Agharanya reported on the effect that a nutritionally balanced diet containing cassava had on overall endocrine function. Reference has already been made to Nigeria as a situation where goitre and cassava consumption have an apparently causal link; in this connection it is therefore interesting to note a very recent report (by Ijomone *et al.*, 2014) reviewing the histo-pathology of thyroid diseases in Southern Nigeria over a ten year period. Further information on the situation in Nigeria (although its conclusions may be expected to apply wherever cassava products are consumed on a daily basis and in substantial amounts) can be found in the website cited under "interesjournals". A website called *Media Global: Modern Ghana* carries a report titled "Cassava's link to iodine deficiency requires further study", a sentiment reflected in some of what follows in this review, as does the web posting by Ramirez(2004) "Goiter and IDD: not as simple as it gets?"

"Hypothyroidism" refers to situations where the thyroid gland seems to be under performing in terms of its capacity to produce thyroxin, the principal hormone associated with it, and/or the body is not responding normally to the hormone that is available to it. There is increasing evidence that this is becoming more prevalent, particularly in females, in Europe, North America and other regions with similar diets and lifestyles, although the reasons for this are unclear, but it is generally accepted that it is not just a consequence arising from improved diagnostic skills. In these cases there is no suggestion that dietary iodine intake is insufficient (adding an iodide salt to standard food-grade table salt is common practice and the rest of the diet probably provides sufficient iodine even if supplemented table salt is not available) and the diet, if it contains cassava at all (which is usually unlikely) would not be expected to contain it in sufficient quantity to raise any question or concern regarding exposure to clinically significant cyanide levels. This topic is thoroughly explored in Skinner (2003). However, while the term "hypothyroidism" is occasionally found in discussions concerning cyanide levels in diets and other exposure routes to the toxin, this does not seem to equate exactly to the term as it is employed clinically by Skinner and other observers. Thus it is not clear to me if there is any link between very low level chronic exposure to cyanide and hypothyroidism as defined by Skinner; this issue will be explored subsequently, but it seems reasonable to advance the hypothesis that, given the known facts about cassava, cyanide and goitre, there may be a case to argue that chronic, long-term cyanide exposure at very low level might induce some form of classical hypothyroidism. Skinner also stresses the problems in correlating laboratory results such as blood analysis with patients' symptoms, but this does not invalidate measuring the levels of the thyroid hormones (thyroxin and tri-iodothyronine) in blood, and procedures for this analysis are reviewed by Sapin and Schlienger (2003). Also relevant here is the Website "Control of Konzo and kits to monitor cyanide exposure from cassava".

The rest of this article will explore that and related information and conjectures concerning cyanide levels in cassava products and what might be done about the issue. It is however absolutely essential to make it totally clear that I do not attack cassava, instead I raise these issues in order to promote informed debate upon them. Furthermore it must be appreciated that, while potential cyanide concentrations in cassava probably exceed those in any other crop plant, the capacity to release some cyanide is present in other crops (*Diagnosis Diet* (blog); Website *Nutrition and Supplements*, Foods relating to hypothyroidism). I am aware that there is a potential for problems here, and that in the wrong hands this could be elevated to an attack on cassava. The scientists' approach must be that we consider all these issues in a fully informed manner and seek to deal with them in a constructive way that will both protect cassava product consumers, (human and other animals) and safeguard this valuable crop and the industries associated with it. Finally it must be acknowledged that many plants produce other substances that are toxic or "anti-nutritional", including such vital staples as soybeans. The FAO website listed in the References gives access to an on-line text titled *Roots, tubers, plantains and bananas in human nutrition*, Chapter 7 of which is devoted to "Toxic substances and antinutritional factors.

Cassava, the crop

Growing

It is remarkably easy to grow. It does form flowers, and so presumably seed (although I have not found reference to this matter in any source that I have examined) but normal propagation is a simple vegetative system, admirably suited to subsistence farming. As the plants are lifted to harvest the tubers, the long stems that bear the leaves are cut off. These stems can then be cut up into 15 cm. or so lengths and these are then planted. They seem to root readily in moist soil and soon develop into substantial plants. I have seen the view expressed that such a propagation system, while suitable for small scale subsistence farming, could not be mechanized. On the contrary, it seems to me that it would be very easy to devise a simple system whereby a spike would make a hole in the soil, a cutting would be delivered to that hole and a squirt of water would settle the soil around it. The growing plants respond to fertilizers and regular watering just as favourably as any other plant would, but, as previously noted, a reasonable crop can be obtained on fairly poor soil, and also the plant is relatively tolerant to drought, although it is reported that exposure to it increases the linamarin (cyanogenic glucoside) content.

Harvesting

The tubers are simply cut from the plant. This however initiates undesirable (from the processors' and consumers' view) changes in the tubers so it is essential that processing follows on from harvest reasonably quickly.

Processing

The outermost fibrous layer is cut away. The starchy inner material must be detoxified. It contains a substance called linamarin (although in lower concentration than that found in the outer part of the tuber) which, when hydrolysed by the enzyme linamarase, also present in the tuber, releases cyanide and glucose. Other cyanogenic glycosides are also present, but linamarin is the principal one and to save repetition the subsequent discussion will refer only to it. Steinkraus (1996, 2004) states that the whole tuber contains around 300 ppm HCN, but the core yields around 160 to 180 ppm HCN. Thus the outer fibrous layer has a higher linamarin level than the core; Steinkraus (2004) states that the peelings contain 660 ppm cyanide. The core is then processed to reduce the cyanide content; the process varies somewhat depending on local practice but the intention is always to maximise contact between linamarin and linamarase, so that the former is converted to its component parts. Typically the flesh is grated or cut into cubes, then this product may be placed into sacks and squeezed, immersed in water, etc. Steinkraus (1996) states that in *gari* (a Nigerian product) processing, the material after grating has already lost some cyanide, with about 100 ppm remaining and the subsequent fermentation reduces this to 52 ppm. During the fermentation the linamarase continues to process the linamarin and a microflora develops, principally comprising lactic acid bacteria (LAB) but with other components such as yeasts also present. Linamarase has an optimal pH for activity around 5.5, rather lower than the fresh plant tissue, but the lactic fermentation reduces this to the enzyme's optimum, then eventually to 4.0 to 4.2. This acidification is highly desirable as it shifts the equilibrium between the ionized and unionized HCN in favour of the latter, so promoting loss of cyanide from

the plant material to the atmosphere. Thus the pulp mash pressed after fermentation contains around half the cyanide present before fermentation and the juice expressed from the pulp has about 85ppm cyanide. In gari production the pulp is then sun-dried and roasted (garification) to further remove cyanide while developing the flavour and colour associated with the product. Steinkraus (2004) states that freshly prepared gari contains around 23ppm cyanide, but typically marketed product has around 10ppm and storage for 4 months can reduce this to 3ppm. It must also be noted that linamarin, linamarase and hence the prospect for cyanide production are present throughout the plant, thus Steinkraus (2004) quotes the fresh leaf as having 2010 ppm cyanide, which reduces after cooking to 85 ppm.

Interpreting the above numbers can be a little difficult, but the most reasonable suggestion would seem to be that they represent the total of the free and bound cyanide present in the material being discussed.

Hydrogen cyanide in the processing environment

There seems to be little reliable data on this important matter. Again we must refer to Steinkraus 1996, who states that the concentrations in the air are:-

Peeling machine 2 ppm

Grating machine 10 ppm

Fermentation tanks Nil

Granulator Nil

Obviously in any real situation these levels will depend on many factors, including the quantities being processed, enclosed or open environment, amount of air movement, etc. It seems highly improbable that the atmospheric levels of this very poisonous material are not routinely monitored in the larger facilities producing processed cassava (typically tapioca) for export or quantity retail, but I have not so far found information on this. It is of course highly unlikely that any regard to this matter is taken at village or domestic level production.

The United Kingdom Health and Safety Executive 8 hours TWA Exposure Limit for cyanides is 5 mg. per cubic metre of air, and for HCN 1.1 mg. per m³ equates to 1 ppm. This is a convenient benchmark for this discussion but we must recall that, as noted above, there seems to be some confusion in published material concerning permissible exposure levels for workers in environments where cyanide(s) will be present in the air that they are breathing.

While not strictly analogous to the cassava processing industry it may be noted that in an Indian study concerning exposure to atmospheric cyanide by workers in an industrial setting where electrical cables were being processed. Banerjee *et al.* (1997) found that operatives' blood showed elevated levels of thiocyanate. This material results from the body's attempt to detoxify the cyanide, although even this "detoxification" product can be harmful to the thyroid gland.

Cyanide toxicity and goitre

Acute cyanide toxicity results from the ion forming complexes with metal ions that are vital as cofactors for various enzymes, particularly respiratory chain enzymes, thus abolishing their function and causing serious problem with the body's energy supply and eventually (very quickly if the concentration is sufficient) convulsions and death.

The interaction with the thyroid gland at low cyanide concentration is somewhat different. As previously noted iodine is essential to form the hormone thyroxin. In fact the gland forms two versions of the hormone, one containing 4 iodine atoms, and the other has 3 atoms. The immediate product from the gland apparently comprises about 85% of the former product and the rest is the version with 3 iodine atoms; it is this latter version that is essentially the active hormone, although the I-4 version has some activity. As these molecules circulate through the body the I-4 version is deiodinated to the I-3 active molecule as the body requires it. The pineal gland monitors blood thyroxin levels and produces thyroid stimulating hormone (TSH) if it decides that too little of the hormone is present. In goitre the demands made upon the thyroid gland are excessive for obvious reasons, and so, in its attempt to respond to the situation the gland becomes enlarged, the classical symptom of goitre. This brief description of the relevant biochemistry is largely based on Skinner's account of goitre.

The cyanide ion is remarkably like the halide ions (fluoride, chloride, bromide, iodide) in much of its chemistry, and this is the key to its effect on the thyroid gland; in essence it interferes with the functioning of the enzymes whose task it is to insert the iodine atoms into the hormone.

Thus, while the chemistry is different, goitre due to dietary iodine deficiency and that due to exposure to low levels of cyanide in the diet are probably clinically indistinguishable from each other. For the victim the effects are identical, lethargy, decreased mental function that in the classical chronic case can be so extreme as to known as "cretinism" in older literature lacking modern sympathies, and a whole range of other effects that in total give a very poor quality of life.

Hypothyroidism

While goitre is a very evident and easily diagnosed condition in most cases, hypothyroidism is much more subtle and difficult to quantify. Indeed its prevalence in the more affluent parts of the world, and even its reality as a clinical manifestation, have both caused much debate, some of it acrimonious. This is complicated by the fact that biochemical analyses (principally for thyroxin and TSH) and the patient's symptoms may present divergent results, or in plainer English the clinician and the laboratory biochemist may reach very different conclusions.

If this is the case for more affluent societies, then it may be surmised that in the sort of developing countries where cassava is being produced, processed and consumed as a dietary staple, the chance that the under-resourced and stressed clinicians (if any are available) will not have the time to spend on the sometimes lengthy interactions with patients that seem to be a prerequisite for diagnosing hypothyroidism, and also support from laboratory blood analyses (requiring radioactive iodine), may not be available. On the other hand "absence of evidence is not evidence of absence" and it would seem reasonable to suggest that chronic exposure to low concentrations of dietary cyanide *could* result in those so exposed having symptoms that would justifiably generate a diagnosis of hypothyroidism. In this matter it should be observed that the report describing the careful clinical work by Banerjee *et al.* (1997) on workers exposed to cyanide fumes in an industrial setting does not include information such that we might make deductions about the subjects showing symptoms consistent (or not) with hypothyroidism.

Vitamin B12

There is a strong link between hypothyroidism and vitamin B12 deficiency in the sense that each will make the symptoms arising from the other deficiency worse, and there is also an impression that cyanide intoxication and B12 deficiency will have synergies. When we consider that vitamin B12 is normally only available to us from eating animal products (an important exception is the Indonesian food called *Tempe*) and that the consumer most reliant on cassava as a daily staple is unlikely to eat much animal protein, because of financial constraints, this will suggest the possibility that further problems will exist for those consumers. The Website *Progressive Health* provides some useful background in a piece titled "What is vitamin B12?"

The symptoms associated with hypothyroidism

The list is long and complicated, and Skinner (2003; from whom this is taken) emphasises that each individual is different and so the actual symptoms seen in each case will be characteristic for that case, therefore the presence or absence of any one symptom does not of itself determine if the patient is hypothyroid. His symptoms list, in addition to the chronic, and sometimes intense fatigue and the problems with cognitive function already referred to, also mentions that patients experience problems with controlling their emotions, show characteristic changes in appearance, both to general body presentation and more specifically to the facial expression (he refers to this as the "hypothyroid expression" and notes, perhaps unsurprisingly that a sad, defeated look is the most common version thereof). The voice can also alter, in part (but not entirely) due to the tongue swelling and thickening. Digestive and gastro-intestinal problems will be present, as will ill-defined aches and pains, possible weight gain, menstrual problems and (possibly related) loss of libido. He also mentions palpitations and changes to blood pressure and pulse rate, breathlessness, headaches, problems with body temperature regulation and consequent intolerance to heat or cold, cramping and an enlarged or tender thyroid gland, which last surely borders on classic goitre. Sensory disturbances are commonly experienced, with visual problems sometimes amounting almost to hallucinations and certainly including an impression that something has rushed past the person or is just out of sight, perhaps like an insect or spider in the vicinity. The problem with such a set of symptoms is that they are difficult to assess objectively and there is a real danger that they might be dismissed as trivial or even malingering, although it is difficult to believe that anyone who has talked for any time with someone with clinically validated hypothyroidism could make that last assessment.

What might be done to deal with this situation?

Essentially, what research programmes might be set up to investigate the effects (if any) found in those who work in the cassava industry and those who consume cassava? From what has been written so far it will be obvious that, in my opinion, we need more information on several matters relating to cassava and cyanide.

- What atmospheric cyanide levels are present in environments where cassava is being processed?
- What levels of cyanide and linamarin are present at each stage in the process from newly harvested cassava to finished product?
- What thiocyanate and free cyanide levels are present in the blood of workers in the processing environment?
- Can cyanide at levels too low to cause goitre still cause problems for those eating it regularly? More specifically can there be a link between cyanide exposure at low concentrations and hypothyroidism?
- What cyanide levels are present in wastes (such as peelings from the tubers) and liquid wastes such as press juice and the residual water from tank processing? Can their handling be bettered to reduce or even eliminate any problems?
- What microbes can utilize cyanide and is/are any of them suitable for removing residual cyanide from processed products? In particular can they be introduced during the tuber processing and will this enhance protein levels in the processed cassava?
- Is there any evidence that animals that are feeding on tapioca show symptoms consistent with hypothyroidism?
- Does the Thai cassava industry have information relating to any of the questions that are listed above? These are very sensitive issues and they must be handled with great care and delicacy, but it is my belief that no good ever comes from avoiding such issues, whereas dealing with them openly will lead to good solutions that will benefit the industry's development. I have already made it clear that in my opinion cassava has a very good future; it is growing in production and importance when previous experience would lead us to expect that increasing affluence will result in decreasing demand for it. The reasons why this is happening are not clear to me, but someone who understands crop economics may be able to develop the explanation for this. Whatever the reasons, we should be pleased about it and Thailand, as the world's leading cassava products exporter, surely must take the lead in solving the problems that the crop presents to us; their solution will support the industry's future development, whereas ignoring them will eventually impact badly on it.

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